

DISCUSIÓN

11.1 Aislamiento de las motoneuronas espinales del embrión de pollo

Uno de los objetivos principales de este estudio ha sido el desarrollo de un método reproducible y eficaz para aislar y cultivar MTN's de la médula espinal del embrión de pollo. A diferencia de los modelos experimentales *in vivo*, las técnicas de cultivo primario de neuronas permiten el estudio de células nerviosas aisladas y desprovistas de sus relaciones naturales, consiguiéndose así una situación experimental propicia para influir de forma muy controlada sobre el comportamiento de dichas células. Por tanto, pueden ser muy útiles a la hora de identificar las entidades moleculares presentes en el tejido muscular esquelético con capacidad para estimular la supervivencia de las MTN's durante el desarrollo embrionario. Sin embargo, la metodología *in vitro* presenta varios inconvenientes que, en ocasiones, pueden conducir a conclusiones erróneas. Por ejemplo, la presencia de células gliales en cultivos neuronales es una fuente potencial de artefactos dado que pueden liberar moléculas capaces de influir sobre las células neuronales. Por otra parte, el aislamiento de las células neuronales de su entorno natural puede dificultar la interpretación de los fenómenos observados *in vitro* así como enmascarar otros. Por estos motivos, los resultados obtenidos *in vitro* siempre deben ser confirmados *in vivo*.

Han existido diversos intentos de conseguir preparaciones celulares enriquecidas en MTN's espinales embrionarias donde poder estudiar sus requerimientos neurotróficos. En primer lugar, se desarrollaron cultivos de disociados de médula espinal sin ningún fraccionamiento (Varon y Raiborn, 1969; Giller et al., 1973, 1977; Adler et al., 1979b). Estos cultivos presentaban el gran inconveniente de estar integrados por células de naturaleza neuronal y no neuronal y con morfologías muy diferentes. Para poder examinar la supervivencia de las

MTN's en cultivo, se desarrollaron diversas técnicas dirigidas a diferenciar estas neuronas del resto de células de la médula espinal, como el marcaje retrógrado de las MTN's mediante el transporte retrógrado de peroxidasa de rábano (Bennett et al., 1980; Slack y Pockett, 1982; Tanaka y Obata, 1983; Nurcombe et al., 1984) o de colorantes fluorescentes (Calof y Reichardt, 1984; Eagleson y Bennett, 1986; Honig y Hume, 1986; O'Brien y Fischbach, 1986a; Dohrmann et al., 1986; Smith et al., 1986). Asimismo, se emplearon diferentes marcadores específicos (captación de colina, componentes de la superficie celular, enzimas sintetizadores de neurotransmisores, etc.) para diferenciar las MTN's del resto de las células presentes en el cultivo (Giller et al., 1977; Brookes et al., 1980; Cozzari y Hartman, 1980; Kaufman et al., 1985). Por otra parte, también se desarrollaron métodos de selección de MTN's basados en técnicas de disección en estadios muy precoces del desarrollo embrionario (Berg y Fischbach, 1978; Masuko et al., 1979; Henderson et al., 1981, 1983; Longo et al., 1982; Smith et al., 1985). No obstante, en general todas estas metodologías presentaban una gran limitación: la consecución de porcentajes de enriquecimiento en MTN's relativamente pequeños.

En los estadios precoces del desarrollo embrionario (por ejemplo, en el día E5,5 del desarrollo embrionario del embrión de pollo) las MTN's son las células de menor densidad de flotación en la médula espinal. Esta propiedad ha permitido el desarrollo de métodos de purificación de MTN's espinales basadas en el empleo de técnicas de sedimentación de suspensiones celulares preparadas a partir de médulas espinales de embriones de pollo o de rata sobre gradientes de densidad (conseguidos mediante diluciones de metrizamida, sucrosa o sucrosa/Ficoll). Esta técnica, descrita originalmente por Schnaar y Schaffner (1981), ha sufrido diversas modificaciones posteriormente (Dohrmann et al., 1986; Arakawa et al., 1990), y ha sido ampliamente utilizada para purificar esta población de neuronas de embriones de rata, ratón y pollo (Flanigan et al., 1985;

Dohrmann et al., 1986, 1987; Arakawa et al., 1990; Caroni y Grandes, 1990; McManaman et al., 1990; Jeong et al., 1991; Juurlink et al., 1991b; Martinou et al., 1989, 1992; Hughes et al., 1993a; Milligan et al., 1994), obteniendo resultados significativamente mejores que con las otras técnicas anteriormente descritas.

Con la intención de conseguir cultivos puros de MTN's, pusimos a punto un método de purificación de MTN's espinales de embriones de pollo de 5,5 días de edad mediante una técnica de sedimentación en un gradiente de metrizamida. La metodología empleada fue esencialmente la descrita por Arakawa et al. (1990) con algunas modificaciones menores (véase Apartado 7.1.2). Utilizamos metrizamida -una sucrosa modificada- para generar los gradientes de densidad, dado que, a diferencia de la sucrosa o las mezclas de sucrosa/Ficoll, consigue generar gradientes en el rango de densidad apropiado sin generar grandes gradientes de osmolaridad o viscosidad que pudieran afectar la integridad celular (Schnaar y Schaffner, 1981).

Nuestra técnica de purificación permite obtener una población pura (>95%) de MTN's, según criterios morfológicos, bioquímicos e inmunocitoquímicos. La población de MTN's purificada está compuesta por células de morfología homogénea y con un diámetro medio de 13,13 μm (Figura 8.1), que coincide con el que presentan las MTN's de la columna motora de la médula espinal *in vivo* (J.E. Esquerda y J.X. Comella, comunicación personal). También se determinó la actividad ChAT -un marcador fiable para las MTN's-, detectándose aproximadamente un 70% de la actividad total de ChAT en la fracción de MTN's (Figura 8.2). En cultivo, las células de esta fracción se diferencian adquiriendo una morfología neuronal típica con una emisión profusa de elongaciones neuríticas con patrón multipolar y la expresión fenotípica de marcadores neuronales (Figura 8.3).

El rendimiento neto de MTN's obtenido con nuestra técnica de purificación fue de 103.877 ± 7.652 células por médula espinal ($n = 22$), con un porcentaje de viabilidad mayor del 97%. Este número equivale aproximadamente al número total de MTN's presentes en la médula espinal del embrión de pollo en E6, según se determinó mediante estudios histológicos cuantitativos (Hamburger, 1975; Oppenheim et al., 1978; Oppenheim y Majors-Willard, 1978; Laing, 1982). Por otra parte, este resultado está en desacuerdo con el de Schnaar y Schaffner (1981), quienes determinaron que su fracción enriquecida en MTN's contenía al menos 400.000 células por médula espinal.

Uno de los inconvenientes de nuestra técnica de purificación de MTN's es que una proporción significativa de MTN's es destruída durante el proceso de aislamiento. Adicionalmente, un 30-40% de las MTN's purificadas muere durante las 24 hr iniciales de cultivo. Diversos investigadores han intentado desarrollar métodos menos agresivos para aislar MTN's espinales. Por ejemplo, tras marcar las MTN's retrógradamente con un trazador fluorescente, es posible separar las células marcadas mediante técnicas de citometría de flujo (Calof y Reichardt, 1984; Eagleson y Bennett, 1986; O'Brien y Fischbach, 1986; Martinou et al., 1989). Sin embargo, esta metodología no ha resultado ser muy útil, dada la gran variabilidad en la abundancia y el grado de integridad de las MTN's descritas por los diferentes investigadores.

Mucho más prometedores han sido los resultados obtenidos con la técnica de purificación de MTN's por *immunopanning* (Bloch-Gallego et al., 1991; Camu y Henderson, 1992; Henderson et al., 1993a). En esta técnica, las MTN's son seleccionadas a partir de un disociado celular de médula espinal ventral de embrión de rata o pollo, aprovechando la interacción con anticuerpos monoclonales dirigidos contra un antígeno de la superficie celular altamente específico para las MTN's (por ejemplo,

p75 o SC1) previamente inmovilizados sobre la superficie de una placa de cultivo. Este método permite aislar MTN's espinales viables y con un alto grado de pureza (>90%).

11.2 La muerte de las motoneuronas por privación de extracto muscular es apoptótica

Desde hace tiempo se conoce que los extractos solubles de tejido muscular no purificados contienen actividad(es) trófica(s) capaces de estimular la supervivencia de las MTN's tanto *in vitro* como *in vivo* (revisado en Apartado 2.5). En nuestra estrategia experimental hemos utilizado extractos de músculo denervado dado que la denervación incrementa el contenido total de actividad trófica para MTN's (Henderson et al., 1983; J.X. Comella y C. Sanz-Rodríguez, datos no publicados), probablemente como consecuencia de un aumento de los niveles de moléculas de ARNm para el supuesto factor trófico (Rassendren et al., 1992). Las MTN's muestran una estricta dependencia del MEX para su supervivencia *in vitro*, de forma que cuando son cultivadas en medio sin MEX mueren cerca del 60-70% en un plazo de 2-3 días (Figura 8.3D).

Por contra, en presencia de MEX las MTN's son capaces de mantener un buen nivel de supervivencia incluso después de 6 días de cultivo (Figura 8.3A,B). Sin embargo, a partir del 7º día de cultivo, el número de MTN's disminuye progresivamente de forma que en el día 9º sólo el 20% de las neuronas siguen vivas. La pérdida de capacidad del MEX para mantener la supervivencia de las MTN's a partir del 6º día de cultivo podría reflejar un cambio en los requerimientos tróficos de las neuronas. Inicialmente, las MTN's tendrían sus requerimientos tróficos satisfechos por el MEX, pudiendo seguir un programa de diferenciación similar al que se ha descrito *in vivo*. Más tardíamente, aparecerían nuevos requerimientos tróficos. No se debe olvidar que el desarrollo de las proyecciones aferentes supraespinales y musculares de las MTN's

lumbosacras es relativamente tardío *in vivo* (después de E13) (Oppenheim, 1975; Lee y O'Donovan, 1991), y cabe la posibilidad de que estas aferencias añadan algunos requerimientos adicionales para la supervivencia, quizás a través de un cambio en el patrón de estimulación eléctrica de las MTN's. De hecho, al evitar que las aferencias descendentes supraespinales o sensoriales primarias contacten con las MTN's *in vivo*, se induce la degeneración del 20-35% de las MTN's lumbosacras entre E10 y E16, aunque no se modifica el número de MTN's al final del período de muerte fisiológica de las MTN's (E10) (Okado y Oppenheim, 1984; Oppenheim et al., 1992a).

Uno de los principales objetivos de este trabajo es la caracterización de la muerte de MTN's tras la deprivación de MEX. Las MTN's deprivadas de estímulos tróficos, tras haber emitido inicialmente elongaciones neuríticas incluso de gran longitud, comienzan a mostrar signos de atrofia, que se siguen rápidamente de la degeneración, condensación y fragmentación de los somas celulares a lo largo de las siguientes 24-48 hr. Las neuritas se adelgazan progresivamente hasta hacerse discontinuas. Por último, los restos neuronales acaban desprendiéndose de la placa de cultivo. A nivel morfológico, la muerte de las MTN's deprivadas de MEX parece apoptótica. Cuando se cuantifica con un colorante nuclear la proporción de MTN's moribundas con cambios nucleares sugestivos de apoptosis -condensación y fragmentación de la cromatina nuclear-, se observa un incremento considerable en el número de neuronas apoptóticas en relación con la deprivación neurotrófica (Figura 8.5G).

A nivel ultraestructural, la mayoría de las MTN's moribundas presentan rasgos característicos de la apoptosis, como la condensación del citoplasma con pérdida de la membrana nuclear, la fragmentación cromatínica y la integridad de la membrana citoplasmática (Figura 8.5D-F). Sin embargo, estos cambios aparecen de forma

asincrónica, coexistiendo neuronas en muy diferentes estadios de involución morfológica en el momento en que realizamos el análisis morfológico. Estos van desde células de aspecto sano a otras con un elevado grado de desintegración. Aunque en base a estas observaciones no se puede descartar la existencia de diferentes tipos de muerte de las MTN's en relación con la privación de MEX *in vitro*, al menos algunas de las fases de degeneración de uno de esos tipos de muerte son típicamente apoptóticas.

Aunque no es posible describir una secuencia definitiva de degeneración a partir de observaciones morfológicas estáticas, la siguiente descripción es probablemente una aproximación razonable a lo que ocurre realmente en base a una comparación con observaciones de la secuencia de muerte celular programada *in vivo* (Chu-Wang y Oppenheim, 1978a; Clarke, 1990). El primer signo de degeneración sería la morfología irregular del núcleo. A continuación, aparecerían imágenes apoptóticas, como un citoplasma electrón-denso y la agregación de la cromatina en una o más áreas del núcleo. Progresivamente se iría produciendo la fragmentación de las células apoptóticas, apareciendo acúmulos de detritus electrón-densos rodeados por finos procesos celulares. Por último, los restos de las células muertas serían fagocitados por células con aspecto de macrófagos.

La aparición de un patrón escalonado de degradación del ADN como consecuencia de la intervención de una actividad endonucleásica no lisosómica es un fenómeno molecular claramente relacionado con la muerte celular apoptótica (revisado en Apartado 6.3), de forma que cuando se analiza el ADN de células apoptóticas mediante electroforesis en geles de agarosa se observa un típico patrón escalonado (Arends et al., 1990). Mediante una estrategia diseñada por Edwards et al. (1991) basada en la utilización de técnicas de *Southern blotting*, hemos observado dicho patrón de fragmentación del ADN en las MTN's

deprivadas de MEX, aunque no en aquéllas cultivadas en presencia de MEX (Figura 8.6). Esta evidencia experimental también contribuye a la definición del proceso de muerte de las MTN's tras la deprivación trófica como apoptótico. El análisis del patrón temporal de degradación del ADN rebasaba los objetivos de este estudio. Nuestros resultados, junto con los de otros investigadores (Edwards et al., 1991; Batistatou y Greene, 1991, 1993; Deckwerth y Johnson, 1993; Pittman et al., 1993; Edwards y Tolkovsky, 1994; Ferrer et al., 1994; Mesner et al., 1995), sugieren que el patrón escalonado de degradación del ADN constituye un fenómeno generalizado del proceso de muerte neuronal tras la deprivación trófica.

11.3 El programa de muerte celular se activa de forma transitoria tras la deprivación neurotrófica

Se ha demostrado que el proceso de muerte neuronal tras la deprivación trófica no es meramente un proceso pasivo, sino uno activo que requiere la síntesis *de novo* de ARN y proteínas (revisado por: Johnson y Deckwerth, 1993). La inhibición farmacológica de la actividad traduccional y transcripcional evita la muerte *in vitro* de células neuronales dependientes del NGF (Martin et al., 1988; Edwards et al., 1991; Pittman et al., 1993) así como de otros tipos neuronales dependientes de otros factores neurotróficos diferentes del NGF (Scott y Davies, 1990; Edwards et al., 1991; Mesner et al., 1992; D'Mello et al., 1993; Fahrbach et al., 1994; Harvey et al., 1994; Svendsen et al., 1994; Kubo et al., 1995). Estos hechos sugieren que éste es un fenómeno generalizado que afecta a neuronas con requerimientos tróficos totalmente diferentes.

Asimismo, existe evidencia experimental de que este proceso ocurre bajo condiciones fisiológicas dado que la muerte fisiológica de las MTN's y de las neuronas de los ganglios espinales puede ser evitada *in vivo* mediante la inhibición de la síntesis de proteínas y ARN (Oppenheim et al., 1990). En nuestro modelo de cultivo de MTN's, también hemos

comprobado como la síntesis macromolecular es necesaria para que las neuronas mueran en relación con la deprivación trófica *in vitro*. Al tratar cultivos de MTN's deprivadas de MEX con inhibidores transcripcionales o traduccionales, se consigue inhibir eficientemente la muerte neuronal (Tablas 8.1 y 8.2). Asimismo, la CHX es capaz de bloquear el aumento en el porcentaje de núcleos apoptóticos y la fragmentación oligonucleosomal del ADN en relación con la deprivación neurotrófica (Figura 8.6). Por otra parte, de forma similar a lo que describieron Martin et al. (1988) en relación con la muerte de neuronas simpáticas por deprivación trófica, la función lisosómica no está implicada en los mecanismos que subyacen la muerte de las MTN's tras la deprivación de MEX (véase Apartado 8.4).

En conjunto, todos estos resultados indican que una de las principales funciones de una molécula neurotrófica es la de suprimir un programa de muerte celular en las neuronas. La muerte neuronal fisiológica puede ser conceptualizada como un proceso activo, reflejo de la expresión de un programa de autodestrucción de la célula capaz de ser suprimido por las moléculas neurotróficas. Se han propuesto diferentes modelos para explicar la inhibición de la muerte neuronal por el bloqueo de la síntesis macromolecular (revisado por: Johnson y Deckwerth, 1993).

Una primera hipótesis propone que el programa letal activado por la deprivación neurotrófica estaría integrado por la expresión de genes específicos denominados "suicidas" o *tanatogenes*, y la consiguiente síntesis de proteínas "asesinas" o *tanatinas*, que en última instancia matarían a la célula neuronal de una forma activa (Johnson et al., 1989). No obstante, el requerimiento de síntesis de ARN y proteínas no necesariamente significa que debe producirse la expresión *de novo* de un(os) gen(es) en las células moribundas.

Una segunda posibilidad es que el/los tanatogene(s) y la(s) tanatina(s) sean especies de vida media corta, expresada(s) de forma constitutiva y sintetizada(s) continuamente. Los factores neurotróficos inducirían la degradación de dichas especies de ARNm's y proteínas, mientras que la privación de factor neurotrófico conduciría a una acumulación de tanatinas (Deckwerth y Johnson, 1993). Por otra parte, algunos factores transcripcionales cuya participación en los mecanismos de la apoptosis ha sido demostrada (como *c-fos* y *c-myc*; revisado en Apartados 6.5.5 y 6.5.6.1, respectivamente) cuentan con especies de ARNm de degradación rápida (Rabbitts et al., 1985; Saraban et al., 1988). También se ha sugerido que las endonucleasas podrían actuar de esa forma (McConkey et al., 1990b; Gaido y Cidlowski, 1991).

Una tercera posibilidad es que en las neuronas esté presente de forma constitutiva una forma inactiva de la tanatina con una tasa de degradación muy lenta. Al producirse la privación neurotrófica, se ocasionaría la activación de la tanatina mediante un mecanismo posttraduccional a través de uno o varios productos génicos, que a su vez se sintetizarían *de novo* o se estabilizarían, haciendo así el proceso de activación del programa apoptótico dependiente de la síntesis macromolecular. Estos tres mecanismos podrían coexistir en una misma célula neuronal. De hecho, se ha demostrado la capacidad de las NT's para rescatar las neuronas de su muerte programada a través de mecanismos aparentemente posttraduccionales (Edwards et al., 1991).

En cualquier caso, en sentido estricto no es posible demostrar de forma directa mediante una estrategia farmacológica que el tratamiento de MTN's privadas de MEX con inhibidores de la síntesis de ARN bloquee la regulación transcripcional de genes de muerte. La demostración consistiría en la constatación de que, tras mantener MTN's privadas de MEX en presencia de inhibidores de la síntesis de ARN, es posible rescatarlas con MEX de la muerte inducida por la reanudación de

la actividad transcripcional. Sin embargo, no hemos sido capaces de revertir las acciones de dichas drogas (ActD, CAMP y CORD), incluso a pesar de lavar intensamente los pocillos de cultivo. Las MTN's mueren tras 2-3 días de exposición a cualquiera de estas sustancias, incluso en presencia de MEX.

Hemos interpretado estos resultados como una evidencia de que los inhibidores de la síntesis de ARN son muy tóxicos para las MTN's. Otros dos laboratorios independientes (Martin et al., 1988; Scott y Davies, 1990) han descrito un efecto similar para la ActD sobre otras poblaciones neuronales. Martin et al. (1988) describieron que las neuronas simpáticas expuestas a ActD durante 24 hr perdían la capacidad de incorporar aminoácidos marcados con ^{35}S en la fracción proteica precipitable con TCA, incluso tras un lavado exhaustivo de los cultivos. Scott y Davies (1990) documentaron como tres poblaciones neuronales diferentes eran incapaces de extender neuritas cuando se eliminaba la ActD de los cultivos y se añadía el factor trófico apropiado.

En un intento de determinar con precisión la cinética de la muerte de las MTN's inducida por privación neurotrófica, hemos analizado el "compromiso" hacia la muerte de las MTN's mediante diversas estrategias que incluyen la readición de MEX o adición de inhibidores de la síntesis de proteínas y ARN a tiempos variables tras la privación de MEX. Utilizando estas estrategias, hemos establecido que ~10 hr después de la privación de MEX, las MTN's se "comprometen" de forma irreversible hacia la muerte celular (Figura 8.7A). A continuación, establecimos el tiempo que necesitan las MTN's privadas de MEX para sintetizar los productos que inducen su propia muerte mediante la determinación del intervalo máximo de tiempo de privación trófica que se puede retrasar la adición de inhibidores de la síntesis macromolecular a cultivos de MTN's privadas de MEX, observando aún su efecto de rescate de la

muerte neuronal (Figura 8.7B,C). Este tiempo resultó ser de ~10 hr, como el tiempo de “compromiso” letal.

Edwards et al. (1991) han descrito que el NGF es capaz de rescatar neuronas simpáticas privadas de NGF significativamente más tarde que los inhibidores de la síntesis de proteína y ARN (~27 hr vs. ~15 hr, respectivamente). Estos resultados fueron interpretados como indicativos de que el NGF es capaz de modificar a nivel posttraduccional el programa de autodestrucción activado en las neuronas simpáticas privadas de factor trófico. Sin embargo, tanto nosotros como otros investigadores (Martin et al., 1992) hemos documentado que, cuando las neuronas pierden su potencialidad para ser rescatadas de la muerte mediante la inhibición de la síntesis de proteínas y ARN, también pierden la capacidad de ser rescatadas por su factor trófico específico (Figura 8.7A-C). Por tanto, creemos que, aunque pueda existir un mecanismo de modulación del programa de muerte celular activa, en el caso de las MTN's esta modulación no sería ejercida por el propio factor trófico derivado del músculo.

Otra cuestión de gran interés es determinar si en las neuronas privadas de estímulo trófico el programa de autodestrucción se activa de forma permanente o no. Teniendo en cuenta que la CHX es capaz de mantener la supervivencia neuronal durante períodos de tiempo prolongados, si la activación del programa de muerte celular fuese permanente, al eliminar la CHX del medio de cultivo el programa de muerte celular progresaría ocasionando la muerte de las MTN's independientemente del tiempo de exposición a la CHX. Lógicamente, dicha progresión debería ser bloqueada por las actividades neurotróficas presentes en el MEX independientemente del tiempo de privación trófica y de inhibición de la actividad traduccional.

Con la intención de comprobar esta hipótesis, realizamos experimentos en los que, tras privar las MTN's de MEX, se inhibió durante períodos de tiempo variables la síntesis de proteínas sin interferir con la transcripción directamente. Cuando se utilizó MEX para rescatar las MTN's de la muerte inducida por la reanudación de la actividad traduccional, las neuronas mostraron una respuesta de supervivencia bifásica en función del tiempo de exposición a la CHX (Figura 8.8). Inicialmente (hasta 15 hr), las MTN's murieron al substituir la CHX por MEX. El MEX rescató la mitad de las MTN's después de ~10 hr de iniciar la inhibición de la síntesis proteica. Sin embargo, a partir de 15 hr de exposición a CHX, las neuronas se mostraron progresivamente más resistentes a la muerte celular al substituir la CHX por MEX.

Interpretamos estos resultados como indicativos de que las moléculas de ARNm que codifican las proteínas tóxicas se expresan sólo temporalmente. Hasta 15 hr después de la privación, el MEX no es capaz de revertir el programa de muerte al haberse producido una acumulación de moléculas de ARNm para proteínas tóxicas en el interior de las células como consecuencia de la privación trófica. Al reanudar la síntesis proteica, los transcritos de ARNm acumulados se traducen originando proteínas funcionales capaces de causar la muerte celular. Sin embargo, a partir de 15 hr tras la privación trófica el MEX recupera su capacidad de rescatar la mayoría de las MTN's de la muerte celular porque, probablemente, ya ha cesado la transcripción de al menos uno de los ARNm's esenciales implicados en la expresión génica del programa de muerte. Asimismo, cabe la posibilidad de que los factores neurotróficos contrarresten el programa de muerte celular a través de mecanismos posttraduccionales, como han sugerido Edwards et al. (1991).

Dado que la activación del programa de muerte neuronal en relación con la privación trófica parece transitoria, es posible imaginar mecanismos adicionales por los que las neuronas podrían evitar la muerte celular al menos temporalmente. Por ejemplo, mecanismos como la despolarización crónica (véase Apartado 10.1) o la activación de la PKA (véase Apartado 8.9) proporcionan a las MTN's una independencia -al menos temporal- de la(s) actividad(es) neurotrófica(s) liberadas por sus tejidos diana de inervación, presumiblemente a través de la activación de vías de señalización intracelular que convergen en algún punto con aquéllas activadas por las NT's. Cuando la duración de esta independencia del aporte trófico excede la expresión transitoria del programa de muerte celular tras la privación trófica, las neuronas son capaces de reactivar el programa trófico a continuación al recuperar el aporte adecuado de factor neurotrófico. Por tanto, éste podría ser considerado el último mecanismo de seguridad capaz de evitar la muerte neuronal irreversible.

11.4 El arabinósido de citosina es neurotóxico para las motoneuronas espinales del embrión de pollo *in vitro*

El AraC es utilizado habitualmente como un agente antimitótico que elimina las células proliferativas mediante la inhibición de la síntesis de ADN (Kufe y Major, 1982). De hecho, el AraC es frecuentemente usado en los cultivos de células no mitóticas para eliminar las células proliferativas como los fibroblastos o las células gliales, así como un agente quimioterápico en el tratamiento de ciertas enfermedades linfoproliferativas. Sin embargo, el AraC también puede afectar a ciertas células sin capacidad para dividirse. *In vitro*, el AraC es más tóxico para las neuronas que otras sustancias antimitóticas (Bustos et al., 1980; Smith y Orr, 1987). Asimismo, los pacientes oncológicos tratados con AraC pueden desarrollar degeneración del SNP y del SNC (Russell y Powles, 1974; Hwang et al., 1985).

Diversos investigadores han usado modelos *in vitro* para examinar los mecanismos que subyacen la neurotoxicidad del AraC, demostrando la capacidad de este fármaco para bloquear específicamente la supervivencia *in vitro* de neuronas postmitóticas sensoriales, simpáticas y parasimpáticas estimulada por factores neurotróficos (Wallace y Johnson, 1989; Martin et al., 1990; Tomkins et al., 1994) así como de las neuronas cerebelosas (Dessi et al., 1995). Adicionalmente, en este estudio hemos demostrado la acción neurotóxica del AraC sobre las MTN's espinales cultivadas de un modo dosis-dependiente con una EC₅₀ de ~2 μM (Figura 8.9A). La muerte de las MTN's inducida por el AraC reúne criterios de apoptosis, asemejándose en gran medida a la desencadenada por la privación de MEX en base a sus características morfológicas y temporales, con la única peculiaridad de que existe un retraso en el inicio de la muerte neuronal desencadenada por el AraC en comparación a la privación neurotrófica (Figuras 8.10 y 8.11). Estas observaciones están de acuerdo con lo que se ha descrito para otras poblaciones neuronales (Martin et al., 1990; Tomkins et al., 1994; Dessi et al., 1995). Todas estas evidencias apoyan la teoría de que un programa de muerte similar podría ser activado en ambos paradigmas experimentales. De hecho, en neuronas tratadas con AraC se observa un aumento de la síntesis de diversas proteínas (entre las que se incluyen proteínas de *shock* térmico, proteínas asociadas al citoesqueleto y otras de identidad desconocida) (Dessi et al., 1995), algunas de las cuales podrían ser parecidas a las descritas en neuronas privadas de factor trófico (Villa et al., 1994).

La neurotoxicidad del AraC parece implicar un proceso específico y necesario para la supervivencia neuronal dependiente de dC, un metabolito pirimidínico con el que el AraC está relacionado a nivel estructural. De hecho, se ha hipotetizado que el desfase observado en el inicio de la muerte neuronal desencadenada por el AraC respecto a la

desencadenada por la privación neurotrófica (Figura 8.10) podría estar relacionado con la neutralización por parte del AraC de un paso intermedio específico (Martin et al., 1990). De forma similar a lo descrito en otras poblaciones neuronales (Wallace y Johnson, 1989; Martin et al., 1990; Tomkins et al., 1994; Dessi et al., 1995), la dC contrarresta de forma específica los efectos neurotóxicos del AraC sobre las MTN's (Figura 8.10B).

La EC_{50} para la acción inhibitoria de la dC sobre la neurotoxicidad de 1 μ M AraC sobre las MTN's espinales embrionarias fue de ~ 100 nM. Dado que se conoce la capacidad del AraC para interferir con la fosforilación intracelular de deoxinucleósidos, se ha hipotetizado que el AraC podría alterar de forma selectiva el equilibrio entre los depósitos intracelulares de trinucleótidos (Balzarini et al., 1987; Wallace y Johnson, 1989; Martin et al., 1990; Tomkins et al., 1994). Sin embargo, se desconoce hasta qué punto este mecanismo es relevante en el control de la supervivencia neuronal, dado que se ha descrito que la perturbación del equilibrio de estos depósitos no tiene un efecto letal sobre las neuronas (Yoshioka et al., 1987). En general, las células tienen dos depósitos de dCTP (Mordoh y Fridlender, 1977; Nicander y Reichard, 1985). Mientras que uno de los depósitos es utilizado por las células para la síntesis de ADN (Spyrou y Reichard, 1987), el otro permite la síntesis de derivados de la dC (Sugino, 1957; Potter y Buettner-Janusch, 1958; Ter Schegget et al., 1971; Medrano y Mordoh, 1979; Spyrou y Reichard, 1987), usados a su vez en la formación de fosfolípidos (Kennedy et al., 1959; Ter Schegget et al., 1971). Dichos fosfoliponucleótidos podrían ser críticos para la supervivencia neuronal. El AraC, al competir con la dC, comprometería esta vía de síntesis, produciendo de forma secundaria la muerte neuronal apoptótica (Wallace y Johnson, 1989; Martin et al., 1990).

Adicionalmente, el AraC es capaz de inhibir diversas actividades enzimáticas, como la ADN ligasa (Zittoun et al., 1991) y la β -ADN polimerasa -un enzima implicado en la reparación del ADN- (Fram y Kufe, 1985). Tomkins et al. (1994) también han sugerido que el AraC podría actuar a través de la inhibición de la topoisomerasa II. El AraC también inhibe la síntesis de glicoproteínas y glicolípidos a través del bloqueo de la incorporación de galactosa, *N*-acetilglucosamina y ácido siálico (Hawtrey et al., 1973, 1974; Klohs et al., 1979; Myers-Robfogel y Spataro, 1980; Hindenburg et al., 1985). Por último, el AraC induce la expresión de genes de respuesta precoz, como *c-jun*, *junB*, *junD*, *c-fos* o *c-myc* (Mitchell et al., 1986; Kharbanda et al., 1991, 1993) y la activación del factor nuclear NF κ B (Brach et al., 1992c).

En resumen, nuestros resultados constituyen una evidencia adicional de la implicación del metabolismo de las purinas y pirimidinas en la supervivencia de los sistemas neuronales. De hecho, recientemente se ha descrito la existencia de un mecanismo bioquímico para la inducción de la muerte neuronal por un deoxinucleósido endógeno en presencia de estímulos tróficos exógenos (Wakade et al., 1995). La profundización en el estudio de estas vías metabólicas proporcionará con toda seguridad nuevas perspectivas sobre los mecanismos de supervivencia neuronal relevantes al desarrollo del SN.

11.5 Las motoneuronas de la médula espinal del embrión de pollo presentan receptores TrkB y TrkC en su superficie

En la literatura han aparecido diversos resultados contradictorios sobre las dependencias tróficas y el patrón de expresión de los receptores para NT's de las MTN's espinales durante el desarrollo embrionario. En el caso de los roedores, el BDNF y la NT-4/5 estimulan la supervivencia de MTN's inmaduras axotomizadas (Sendtner et al., 1992a; Yan et al., 1992, 1993; Henderson et al., 1993a; Koliatsos et al., 1993;

Wong et al., 1993; Li et al., 1994). En este sentido, es de gran interés la constatación de que el tejido muscular esquelético expresa las tres NT's (Maisonpierre et al., 1990b; Henderson et al., 1993a; Koliatsos et al., 1993; Yan et al., 1993). También se ha demostrado el transporte retrógrado del NGF, el BDNF y la NT-3 hasta el soma de las MTN's lumbares cuando se inyectan en nervios ciáticos lesionados de las ratas (Miyata et al., 1986; DiStefano et al., 1992; Yan et al., 1988, 1992, 1993; Koliatsos et al., 1993), aunque sólo las dos últimas tienen acciones neurotróficas sobre las MTN's.

Por tanto, parece evidente que las NT's BDNF, NT-3 y NT-4/5 contribuyen en mayor o menor grado al mantenimiento de la supervivencia de MTN's tanto sanas como lesionadas de la rata. Sin embargo, los resultados publicados hasta la fecha sobre los requerimientos neurotróficos de las MTN's espinales del embrión de pollo *in vitro* son más difíciles de interpretar. Diversos laboratorios han comunicado que las MTN's embrionarias de pollo cultivadas no responden a ninguna NT (Dohrmann et al., 1986; Arakawa et al., 1990; Berkemeier et al., 1991; Bloch-Gallego et al., 1991; Thoenen, 1991). No obstante, la administración de inyecciones diarias de BDNF en la membrana corioalantoidea de embriones de pollo consigue rescatar aproximadamente un tercio de las MTN's que de otra forma hubiesen muerto entre E6 y E10 (Oppenheim et al., 1992a, 1993).

De forma similar, la administración de NT-4/5 durante este período de tiempo consigue rescatar el 10% de las MTN's moribundas (Oppenheim et al., 1993). Otras NT's como el NGF o la NT-3 no parecen tener ningún efecto relevante cuando se utilizan en este sistema *in vivo*. Otro resultado intrigante en este contexto es que las MTN's purificadas a partir de embriones de pollo en E5 son capaces de interactuar en su superficie con la NT-3, pero no con el BDNF o la NT-4/5 (Escandón et al., 1994).

En un estudio recientemente realizado en nuestra Unidad de Investigación (Soler et al., 1997), hemos demostrado la capacidad de las MTN's espinales embrionarias cultivadas para responder a los factores neurotróficos BDNF y NT-3. Interesantemente, las MTN's aisladas a partir de embriones de pollo de 5,5 días de edad no responden a ninguna de estas NT's ni al NGF. Dichos resultados estarían de acuerdo con los hallazgos de otros laboratorios (Dohrmann et al., 1986; Arakawa et al., 1990; Berkemeier et al., 1991; Bloch-Gallego et al., 1991; Thoenen, 1991). Sin embargo, durante los siguientes días de cultivo las MTN's desarrollan una respuesta de supervivencia específica al BDNF y a la NT-3 (Tabla 11.1). En cultivos de 48 hr de antigüedad (equivalente a E8) el BDNF presenta un moderado efecto promotor de la supervivencia de las MTN's, que se hace aún más evidente en cultivos de 72 hr de antigüedad (equivalente a E9). Adicionalmente, la NT-3 también mostró una potente acción estimuladora de la supervivencia de las MTN's en cultivos de 72 hr de antigüedad. El NGF no estimuló la supervivencia de las MTN's espinales en ningún momento.

	E7		E8		E9	
	<u>24 hr</u>	<u>48 hr</u>	<u>24 hr</u>	<u>48 hr</u>	<u>24 hr</u>	<u>48 hr</u>
MEX (300 µg/ml)	100,5 ± 1,9	94,5 ± 3,1	88,9 ± 2,6	81,1 ± 2,4	99,4 ± 1,2	91,6 ± 1,4
Deprivadas	56,9 ± 2,2	40,7 ± 2,9	56,3 ± 2,9	42,9 ± 3,2	75,7 ± 1,9	57,0 ± 2,1
NGF	55,1 ± 2,0	35,0 ± 2,2	51,6 ± 2,0	36,6 ± 2,6	72,0 ± 2,8	67,4 ± 3,2
BDNF	61,8 ± 6,1	50,3 ± 4,0	75,3 ± 3,6	49,0 ± 3,0	85,3 ± 2,3	78,6 ± 2,9
NT-3	59,5 ± 2,2	48,2 ± 2,6	51,7 ± 4,1	46,4 ± 3,0	96,2 ± 2,0	84,2 ± 2,4

Tabla 11.1. La respuesta de las MTN's a las diferentes NT's varía con la edad del cultivo. Se purificaron MTN's a partir de embriones de pollo de 5,5 días de edad y se cultivaron en presencia de MEX (300 µg/ml) durante 24 hr (equivalente a E7), 48 hr (equivalente a E8) o 72 hr (equivalente a E9). Seguidamente, se lavaron los cultivos tres veces con medio basal y se cultivaron durante un período adicional de 24 hr en presencia de 50 ng/ml de las diferentes NT's. Se determinó el número de MTN's en una área definida del pocillo de cultivo en el momento de recambio del medio de cultivo y al final de los períodos de incubación con las NT's. Cada valor de supervivencia representa la media ± SEM de 8 pocillos de un experimento único que se repitió otras dos veces más con resultados comparables a los aquí presentados (adaptado de: Soler et al., 1997).

En coherencia con estos resultados, se ha demostrado como las MTN's expresan ARNm's para los receptores TrkB y TrkC (Henderson et al., 1993a; Koliatsos et al., 1993; Yan et al., 1993). Asimismo, los ratones sin expresión de TrkB y TrkC presentan una significativa reducción en el número de MTN's espinales y faciales (Klein et al., 1993, 1994). Sin embargo, a pesar de todas estas evidencias indirectas de la presencia de los receptores TrkB y TrkC sobre la superficie de la membrana plasmática de las MTN's, los resultados presentados en el Apartado 9 constituyen la primera demostración directa de este hecho. Hemos detectado los receptores Trk en cultivos de MTN's mediante una estrategia basada en la detección de su autofosforilación a nivel de residuos de tirosina en relación con la interacción con NT's específicas. Tanto el BDNF como la NT-3 son capaces de inducir la autofosforilación y, presumiblemente, la activación de los correspondientes receptores Trk, TrkB y TrkC (Figura 9.5), así como de las MAPK's citosólicas (Figura 9.6). La incapacidad de las MTN's de embriones de pollo de 6-7 días de edad para mostrar una respuesta de supervivencia a los factores neurotróficos BDNF y NT-3 se correlaciona con la ausencia de receptores Trk en su superficie. Sin embargo, en MTN's mantenidas en cultivo durante 72 hr (equivalente a E8) ya es posible detectar niveles reducidos de receptores Trk, que se incrementan progresivamente con el tiempo en cultivo (Figura 9.4). Interesantemente, la inhibición de la síntesis de proteínas impide que los receptores Trk aparezcan en la superficie de las MTN's cultivadas (Soler et al., 1997), indicando que se sintetizan *de novo*.

En conjunto, estos resultados sugieren que, en las fases iniciales de la muerte fisiológica, las MTN's embrionarias del pollo no son capaces de responder a las NT's, aunque desarrollan esta capacidad en una fase más tardía de dicho proceso. No obstante, se debe ser extremadamente cauto al extrapolar conclusiones obtenidas *in vitro* a sistemas *in vivo*. No se puede excluir totalmente la posibilidad de que la transición observada

en la capacidad de las MTN's para responder a las NT's sea un artefacto *in vitro*. Por otra parte, las MTN's embrionarias de los roedores expresan moléculas de ARNm para TrkB y TrkC (Henderson et al., 1993a; Ip et al., 1993d) así como receptores funcionales para el BDNF, la NT-3 y la NT-4/5 (Escandón et al., 1994) tan precozmente como en E15, que corresponde al estadio del desarrollo en el que las MTN's de los roedores empiezan a establecer contactos neuromusculares, coincidiendo con el inicio de la muerte neuronal fisiológica. Asimismo, los efectos de estimulación de la supervivencia neuronal del BDNF, la NT-3 y la NT-4/5 sobre las MTN's de roedores se hacen evidentes a partir de E15 (Henderson et al., 1993a; Hughes et al., 1993b). Por consiguiente, parece obvio que se deben realizar estudios más detallados con la intención de aclarar si las MTN's *in vivo* responden a las NT's desde el inicio de su proceso de muerte fisiológica o más tardíamente.

11.6 La autofosforilación de los receptores Trk es necesaria para las respuestas de supervivencia y diferenciación neuronal, aunque de forma diferente

Aparentemente, la autofosforilación a nivel de residuos de tirosina de los receptores Trk guarda una estrecha correlación con la activación de los mecanismos de transducción implicados en la mediación de las acciones biológicas de las NT's. Sin embargo, hasta la fecha la mayor parte de la información sobre las vías de transducción activadas tras la interacción de las diferentes NT's con sus correspondientes receptores de alta afinidad, ha sido obtenida a partir de estudios realizados en células PC12. Las células PC12 responden al NGF mediante su conversión bioquímica y morfológica desde un fenotipo próximo al de las células cromafines a uno más cercano al de neuronas simpáticas, que incluye la emisión y regeneración de neuritas, la excitabilidad eléctrica, cambios en los flujos iónicos y el cese del crecimiento celular (Dichter et al, 1977; Greene y Tischler, 1976, 1982).

El sistema PC12 ha proporcionado un modelo bien caracterizado en el que investigar la diferenciación celular en respuesta al NGF, aunque no permite una aproximación directa al estudio de los mecanismos de transducción relevantes a la supervivencia neuronal dependiente del NGF. Estos estudios han permitido constatar que la autofosforilación a nivel de residuos de tirosina del receptor TrkA es esencial para la diferenciación de las células PC12 inducida por el NGF. No obstante, dado que la supervivencia y la diferenciación de las células neuronales son dos fenómenos muy diferentes, decidimos investigar la relevancia de la autofosforilación de los receptores Trk tanto en la supervivencia como en la diferenciación de células neuronales dependiente de NT's, tomando como modelo cultivos de neuronas simpáticas del GCS de la rata. Estas neuronas característicamente muestran una estricta dependencia del NGF para su supervivencia y diferenciación *in vitro* (Levi-Montalcini y Angeletti, 1963; Greene, 1977a; Chun y Patterson, 1977a, 1977b; Berg, 1982).

La estrategia utilizada consistió, primero, en la identificación de agentes farmacológicos capaces de inhibir la autofosforilación del receptor TrkA y, a continuación, en el estudio de sus efectos a largo plazo sobre la supervivencia y el crecimiento neurítico. Encontramos cinco fármacos con capacidad para inhibir la autofosforilación de TrkA: el K252-a, la MTA, la Herb-A, la estaurosporina y el K252-b, de los cuales utilizamos fundamentalmente los tres primeros por tener mecanismos de acción diferentes y no estar relacionados entre sí a nivel estructural.

Al estudiar los efectos de los inhibidores de la autofosforilación del receptor TrkA sobre el crecimiento neurítico dependiente del NGF, constatamos la existencia de una excelente correlación entre los niveles de activación de TrkA -según se mide por la autofosforilación del receptor- y el crecimiento neurítico (Figura 9.14). La MTA, conocida

clásicamente como un inhibidor de las metiltransferasas, inhibió de modo dosis-dependiente tanto la extensión neurítica como la autofosforilación de TrkA, mostrando unos valores IC_{50} similares y a la vez muy por encima de la K_i de la MTA para la inhibición de las metiltransferasas (Hoffman et al., 1981). Este agente farmacológico, así como otros inhibidores de metiltransferasas, también bloquea selectivamente en las células PC12 la formación de neuritas por mecanismos dependientes e independientes de la transcripción (Seeley et al., 1984), así como la fosforilación a nivel de residuos de tirosina de proteínas intracelulares (Maher, 1988) en respuesta a la exposición al NGF. La Herb-A también es capaz de inhibir el crecimiento neurítico estimulado por el NGF en células PC12 (Muroya et al., 1992a) a unas dosis que bloquean la autofosforilación del receptor TrkA dependiente del NGF.

De forma similar a lo que ocurre con la respuesta de diferenciación, la autofosforilación del receptor TrkA también parece ser necesaria para la respuesta de supervivencia al NGF de las neuronas simpáticas del GCS cultivadas. Cuando se inhibe la autofosforilación de TrkA con el K252-a o la Herb-A -que logran una disminución de la autofosforilación del receptor comparable a la observada en cultivos neuronales deprivados de NGF durante períodos prolongados de tiempo (Figuras 9.10C y 9.12)-, las neuronas simpáticas mueren de una forma que claramente se asemeja a la apoptosis. Sin embargo, aparentemente sólo son necesarios niveles muy reducidos de autofosforilación de TrkA para observar la respuesta de supervivencia al NGF. A una concentración de 2 mM, la MTA inhibe la extensión neurítica completamente pero no la supervivencia, correspondiendo a una inhibición de aproximadamente un 90% de la autofosforilación a nivel de residuos de tirosina de TrkA (Figura 9.13). Asimismo, el K252-a, a una concentración que inhibe la autofosforilación de TrkA en más del 90 %, sólo logra una reducción de la supervivencia de las neuronas del GCS inferior al 30% (Figura 9.10B). Por tanto, en las neuronas estimuladas por sus correspondientes NT's, un

nivel de autofosforilación total a nivel de residuos de tirosina del receptor TrkA de ~10% sería aparentemente suficiente para la señalización de la respuesta de supervivencia, aunque inefectivo para la de diferenciación.

La ausencia de efecto detectada de la MTA sobre la supervivencia neuronal, no está de acuerdo con las observaciones previamente realizadas por Acheson et al. (1986). Estos autores documentaron que la MTA, a una concentración de 3 mM, bloquea de forma selectiva la supervivencia de neuronas simpáticas del pollo dependiente del NGF, hecho que interpretaron como una evidencia de que la metilación proteica representa un paso precoz en la cascada de reacciones iniciada por la interacción del NGF con su receptor. El desacuerdo entre nuestros resultados y los de Acheson et al. (1986) podría ser debido a diferencias en los protocolos experimentales. Mientras que nosotros exponemos primero las neuronas al NGF durante 7 días antes de añadir la droga al medio de cultivo celular, Acheson et al. (1986) expusieron sus cultivos neuronales a la droga poco después de su disociación. No se debe olvidar que la respuesta de supervivencia de las poblaciones neuronales *in vitro* pueden variar con el tiempo de cultivo. Otra posible explicación, aunque menos probable, es que la diferencia entre resultados se deba a una especificidad de especies (rata *versus* pollo) de las vías de transducción activadas por el NGF en las neuronas simpáticas.

En conjunto, los resultados aquí presentados sugieren que la autofosforilación de los receptores Trk como consecuencia de su interacción con las correspondientes NT's es precisa, tanto para el crecimiento neurítico como para la supervivencia neuronal, aunque no de la misma forma. Mientras que se observa una clara correlación entre el grado de autofosforilación del receptor Trk y la respuesta de diferenciación, la respuesta de supervivencia sólo parece precisar niveles muy reducidos de fosforilación del receptor Trk. Este hecho

probablemente refleja que las vías de señalización intracelular implicadas en la mediación de la supervivencia y la diferenciación neuronal divergen muy pronto tras la activación de los receptores Trk.

La autofosforilación de dichos receptores estaría implicada en los mecanismos encargados de generar dicha divergencia. Por ejemplo, en función del grado de activación del receptor se podría producir la fosforilación de residuos de tirosina específicos. A su vez, las diferentes fosfotirosinas resultantes podrían presentar un cierto grado de especialización, de forma que podrían contribuir a la especificidad de la señalización a través de su influencia sobre la actividad kinasa global o de la interacción con substratos individuales. De esta forma, las diferentes fosfotirosinas tendrían una relevancia diferenciada en la mediación de los diversos efectos biológicos desencadenados por las NT's. Por otra parte, las fosfotirosinas presentes en los receptores Trk activados son susceptibles de ser reguladas por fosfatasas intracelulares, configurando así un fino mecanismo de regulación del paso inicial de la transmisión de señales desencadenada por las NT's.

Se han descrito varios casos de especialización de residuos de fosfotirosina en los receptores del PDGF- α y PDGF- β , del G-CSF, de la insulina y los IGF's, del FGF y del EGF (revisado por: Schlessinger y Ullrich, 1992). De forma similar, no todos los sitios de autofosforilación presentes en el extremo carboxi-terminal de los receptores Trk parecen ser igualmente relevantes a la transducción de señales desencadenada por las NT's (Segal et al., 1996). En el caso de TrkA, hay 10 residuos de tirosina presentes en el dominio intracitoplasmático, de los cuales el NGF induce la fosforilación de cinco (Loeb et al., 1994; Stephens et al., 1994; Inagaki et al., 1995). Mediante experimentos de mutagénesis dirigida, se ha demostrado la existencia de tres residuos de fosfotirosina necesarios para la transfosforilación eficaz y eficiente de los residuos de tirosina

implicados en la propagación de la señal neurotrófica (Kaplan y Stephens, 1994). Entre ellos, destacan dos, Tyr490 y Tyr785, que interaccionan al menos con dos proteínas intracelulares, la Shc y la PLC- γ , respectivamente (Mitra, 1991; Obermeier et al., 1993a, 1993b; Loeb et al., 1994; Stephens et al., 1994; Baxter et al., 1995). Por otro lado, la PI-3K parece interaccionar con las tirosinas Tyr 490 y Tyr 751 (Obermeier et al., 1993b; Baxter et al., 1995).

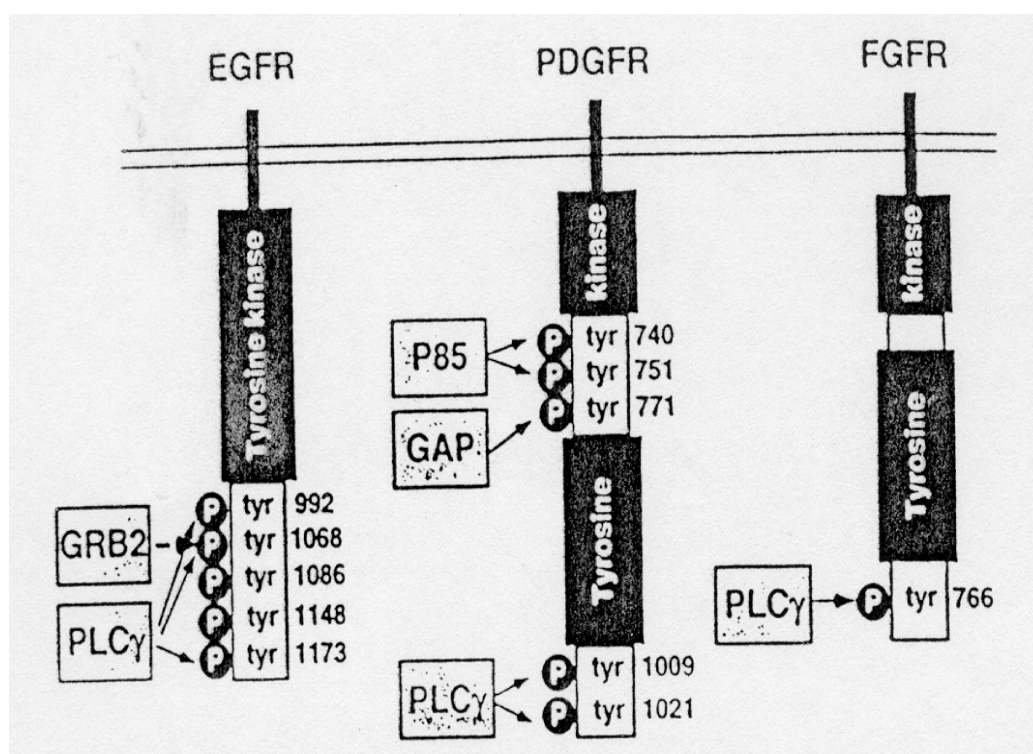


Figura 11.1. Distintas proteínas señaladoras interaccionan con regiones fosforiladas diferenciadas de los dominios intracelulares de los receptores TK (adaptado de: Schlessinger y Ullrich, 1992).

La estrategia farmacológica empleada en este estudio no está exenta de problemas. En general, se debe ser extremadamente cauto a la hora de interpretar las acciones de agentes farmacológicos. En nuestro caso, no se puede excluir totalmente la posibilidad de que el K252-a, la MTA o la Herb-A, además de inhibir la autofosforilación y activación de los receptores Trk, afecten directa o indirectamente una o más kinasas

por debajo de Trk. En el caso concreto del K252-a, se han descrito en la literatura una serie de efectos no explicables a través de la inhibición de la autofosforilación de los receptores Trk. En las células PC12, el K252-a induce un incremento de la transcripción de algunos genes de expresión precoz en ausencia de estimulación neurotrófica (Berg et al., 1992) mientras que potencia ciertas respuestas bioquímicas a diferentes factores de crecimiento (Koizumi et al., 1988).

En este estudio, describimos como concentraciones altas de K252-a son capaces de promover la supervivencia de las neuronas del GCS tanto en presencia como en ausencia del NGF (Figura 9.9), de acuerdo con lo que otros investigadores han documentado en otros tipos neuronales (Borasio, 1990; Glicksman et al., 1995). El K252-a también induce el crecimiento neurítico y la diferenciación neuronal (Glicksman et al., 1993; Maroney et al., 1995). Estas observaciones no pueden ser explicadas por la inducción de la autofosforilación y/o activación TK de TrkA por la droga. De forma similar, mientras que la exposición a la Herb-A causó la muerte de neuronas del GCS estimuladas con NGF, una pequeña proporción de las neuronas parecían tener mejor aspecto que incluso en presencia de NGF sólo (Figura 9.11D).

Otros investigadores, utilizando una estrategia farmacológica, han sugerido también que la supervivencia neuronal y el crecimiento neurítico en respuesta al NGF podrían depender de la activación de vías de señalización diferentes (Volonté et al., 1989; Greene et al., 1990; Volonté y Greene, 1990a). Mediante la utilización de dos análogos de la purina -la 2-AP y la 6-TG-, estos autores han demostrado la participación de al menos tres vías de señalización distintas en la mediación de los efectos del NGF. Además, las acciones de la 6-TG y la 2-AP son independientes de la autofosforilación del receptor TrkA (C. Sanz-Rodríguez y E.M. Johnson Jr., datos no publicados). Por otra parte, el AraC es capaz de bloquear la supervivencia neuronal estimulada por las NT's (revisado en

Apartados 6.4.4 y 11.4), aunque aparentemente no la estimulación del crecimiento neurítico (Greene et al., 1982). Por último, la despolarización crónica de las neuronas evita su muerte por deprivación neurotrófica, aunque no es capaz de estimular el crecimiento neurítico (Franklin et al., 1995).

En conclusión, los resultados presentados en este estudio demuestran que la autofosforilación a nivel de tirosinas de los receptores Trk es necesaria tanto para la supervivencia como para la diferenciación promovida por las NT's. Las vías de señalización intracelular activadas por el receptor Trk, conducentes a la supervivencia y diferenciación neuronal, parecen separarse muy pronto, probablemente al nivel del propio receptor. La autofosforilación de los receptores Trk en relación con la interacción con las NT's podría ser importante para el(los) mecanismo(s) implicados en generar dicha divergencia.

11.7 Los mecanismos de la supervivencia neuronal mediada por Ca^{2+}

Otro de los objetivos de este estudio ha sido el de analizar el efecto de la despolarización crónica sobre la supervivencia de cultivos primarios de MTN's espinales así como algunos de los mecanismos moleculares implicados. La despolarización crónica es capaz de mantener vivas las MTN's deprivadas de estímulos neurotróficos *in vitro*, aparentemente a través del incremento de la $[\text{Ca}^{2+}]_i$ en relación con la activación de canales de Ca^{2+} voltaje-dependientes tipo L (Figura 10.1). La estimulación de la supervivencia neuronal por la despolarización crónica ha sido demostrada en múltiples poblaciones neuronales (revisado en Apartado 5.1).

Los mecanismos mediante los cuales el influjo de Ca^{2+} evita la muerte neuronal por privación neurotrófica no son bien conocidos, aunque pueden ser múltiples y variados (revisado por: Clapham, 1995; Ghosh y Greenberg, 1995; Finkbeiner y Greenberg, 1996). Desde hace tiempo se conoce la actuación del Ca^{2+} como segundo mensajero en la mediación de diversos fenómenos biológicos, como la liberación de neurotransmisores, la inducción de genes de expresión temprana, la activación de proteína kinasas, la activación e inactivación de canales iónicos, etc. La calmodulina es uno de los receptores intracelulares del Ca^{2+} mejor conocidos, habiéndose sugerido su participación en la señalización del efecto de la despolarización crónica sobre la supervivencia neuronal (Gallo et al., 1987; Hack et al., 1993; Franklin et al., 1995; Soler et al., 1997). Tras unirse al Ca^{2+} , la calmodulina activa múltiples proteínas, como la adenilato ciclasa, la calcineurina y varias kinasas y fosfatasas (revisado por: Hidaka e Ishikawa, 1992; Ghosh y Greenberg, 1995). De hecho, las acciones neurotróficas del Ca^{2+} parecen depender de la activación mediada por la calmodulina de la actividad proteína quinasa dependiente de calmodulina tipos I (CaMK-I) (Aletta et al., 1996) y II (CaMK-II) (Hack et al., 1993).

La despolarización crónica de las células neuronales también produce una unión sostenida de la PKC a la membrana plasmática, así como su activación mediada por fosfatidilcolina (Wakade et al., 1988, 1991), mostrando una buena correlación con la supervivencia de las neuronas simpáticas (Wakade et al., 1983). Sin embargo, no parece probable que la PKC participe en la señalización de la supervivencia neuronal en respuesta a la despolarización crónica, puesto que este fenómeno biológico no se ve afectado por la reducción de los niveles de PKC en cultivos de neuronas simpáticas del GCS de la rata (C. Sanz-Rodríguez, J.L. Franklin y E.M. Johnson, Jr., datos no publicados).

La similitud existente entre los efectos de supervivencia de las NT's y de la elevación de la $[Ca^{2+}]_i$ sugiere la existencia de algún punto de convergencia y/o interacción entre las correspondientes vías de transducción. Una posibilidad es que el complejo NT-receptor actúe modulando el influjo de Ca^{2+} . De hecho, las NT's producen una elevación transitoria de la $[Ca^{2+}]_i$ en células neuronales (Pandiella-Alonso et al., 1986; Nikodijevic y Guroff, 1991; Berninger et al., 1993; Zirrgiebel et al., 1995; Zirrgiebel y Lindholm, 1996; Jiang et al., 1997), aparentemente a través de la activación de canales iónicos y de la movilización de depósitos de Ca^{2+} intracelulares. Sin embargo, no parece que las NT's ejerzan su efecto sobre la supervivencia neuronal mediante el incremento de la $[Ca^{2+}]_i$ (Tolkovsky et al., 1990). Las NT's también parecen actuar sobre la homeostasis del Ca^{2+} a través de la regulación de la expresión de los canales de Ca^{2+} (Garber et al., 1989; Plummer et al., 1989; Pollock et al., 1990; Usowicz et al., 1990; Koike y Tanaka, 1991; Lesser y Lo, 1995; Levine et al., 1995; Holm et al., 1997).

Por otra parte, el Ca^{2+}_i también podría actuar a través de la movilización de sistemas de segundos mensajeros responsables de la activación de los receptores de las NT's. Un mecanismo de este tipo ha sido descrito para el receptor del EGF, cuya fosforilación es inducida por el incremento de la $[Ca^{2+}]_i$ (Rosen y Greenberg, 1996). Asimismo, la despolarización crónica podría favorecer la supervivencia neuronal a través de una liberación Ca^{2+} -dependiente de factores autocrinos o paracrinos (Lu et al., 1991; Elde et al., 1991; Ghosh et al., 1994a). Por ejemplo, el BDNF es, al menos parcialmente, responsable de la supervivencia de las neuronas corticales en cultivo estimulada por la despolarización (Ghosh et al., 1994a). No obstante, éste no parece ser el caso ni en las neuronas simpáticas del GCS de la rata (Franklin et al., 1995) ni en las MTN's espinales del embrión de pollo (Soler et al., 1997).

En este estudio, hemos monitorizado la vía de señalización p21ras-MAPK (revisado en Apartado 3.6.2), demostrando que la despolarización crónica tanto de neuronas simpáticas del GCS de la rata como de MTN's espinales del embrión de pollo, induce la fosforilación a nivel de residuos de tirosina de una proteína con un peso molecular aproximado de 42-44 kDa, que parece corresponder a una MAPK (Figura 10.4). Otros investigadores han obtenido resultados similares en cultivos de células PC12 (Tsao et al., 1990; Okumura et al., 1994). Aunque se desconoce a qué nivel la despolarización crónica activa la vía p21ras-MAPK, esto ocurre por debajo de los receptores Trk, dado que la despolarización crónica *per se* no constituye un estímulo suficiente para inducir la autofosforilación y activación de los receptores Trk (Figura 10.3).

Estos resultados han sido recientemente ampliados por otros autores (Bading y Greenberg, 1991; Chao et al., 1992; Rosen et al., 1994; Rusanescu et al., 1995), quienes han demostrado como la elevación de la $[Ca^{2+}]_i$ induce la fosforilación y actividad de las kinasas MEK1 y las MAPK's a través de la activación de p21ras. Hasta la fecha se han descrito tres posibles vías de conexión entre el incremento de la $[Ca^{2+}]_i$ y la activación de p21ras, probablemente interrelacionadas entre sí (revisado por: Finkbeiner y Greenberg, 1996).

La primera conexión se establecería a través de la activación de Pyk2, una proteína con actividad TK que se expresa en el SN (Lev et al., 1995). Al aumentar la $[Ca^{2+}]_i$ se produce un incremento de la actividad y fosforilación de Pyk2, que a su vez induce la activación de la vía de señalización p21ras-MAPK aparentemente a través del reclutamiento de complejos Shc/Grb2/mSOS (Lev et al., 1995; Rusanescu et al., 1995).

Una segunda vía de conexión entre el Ca^{2+}_i y la vía p21ras-MAPK ha sido descrita en las células PC12. El incremento de la $[Ca^{2+}]_i$ induce rápidamente la fosforilación del receptor del EGF, que a continuación

induce la activación de p21ras a través de la interacción con complejos Shc/Grb2/mSOS (Rosen y Greenberg, 1996).

Por último, el tercer mecanismo consistiría en la activación de p21ras por un complejo molecular formado por un factor de intercambio GRF y la calmodulina activada por Ca^{2+} (Shou et al., 1992; Farnsworth et al., 1995). Asimismo, se ha identificado una nueva isoforma de GAP que presenta en su secuencia motivos de unión a la calmodulina (Weissbach et al., 1994; Wes et al., 1996), que también podría intervenir en la regulación de la actividad de p21ras.

11.8 Los requerimientos neurotróficos de las motoneuronas

En los últimos años, se ha demostrado como muchos agentes neurotróficos son capaces de actuar sobre las MTN's *in vitro* o cuando se administran exógenamente *in vivo*. Entre estos, se encuentran el NGF, el BDNF, la NT-3, la NT-4/5, el GDNF, el CNTF, el CDF/LIF, diversas formas de FGF, la insulina y los IGF-I y -II, los PDGF- α y - β , la IL-6, el TGF β y la CT-1 (revisado en Apartado 2.5). Sin embargo, hasta el momento ninguno de estos agentes neurotróficos ha sido identificado inequívocamente como el responsable de la actividad neurotrófica presente en el músculo esquelético encargada de regular la supervivencia de las MTN's tanto durante el desarrollo embrionario como en la edad adulta (revisado por: Henderson, 1996).

A lo largo del desarrollo embrionario, las MTN's espinales presentan una clara respuesta de supervivencia a una gran variedad de factores neurotróficos que se expresan en el tejido muscular embrionario, entre los que se incluyen el BDNF (Bloch-Gallego et al., 1991; Oppenheim et al., 1992a; Hallböök et al., 1993; Henderson et al., 1993a; McKay et al., 1993; Griesbeck et al., 1995; Becker et al., 1997), la NT-3 (Schechteron y

Bothwell, 1992; Henderson et al., 1993a; Hughes et al., 1993b; Griesbeck et al., 1995), la NT-4/5 (Henderson et al., 1993a; Funakoshi et al., 1995; Griesbeck et al., 1995), el GDNF (Henderson et al., 1994a; Oppenheim et al., 1995), el TGF β (Martinou et al., 1990; Flanders et al., 1991; Lafyatis et al., 1991; Millan et al., 1991), los PDGF- α y - β (Oppenheim et al., 1993), los IGF-I y -II (Engstrom et al., 1987; Ishii, 1989; Arakawa et al., 1990; Bondy et al., 1990; Ralphs et al., 1990; Streck et al., 1992; Hughes et al., 1993b; Neff et al., 1993), el CDF/LIF (Martinou et al., 1992; Patterson y Fann, 1992), el FGFa, el FGFb (Joseph-Silverstein et al., 1989; McManaman et al., 1989; Vaca et al., 1989; Alterio et al., 1990; Arakawa et al., 1990; González et al., 1990; Morrow et al., 1990; Fu et al., 1991; Henderson et al., 1993a; Hughes et al., 1993b), el FGF-5 (Hughes et al., 1993a, 1993b) y la CT-1 (Pennica et al., 1996a; Sheng et al., 1996). Sin embargo, de todas estas moléculas sólo unas pocas parecen tener una función relevante durante el período de muerte fisiológica de las MTN's espinales en el embrión de pollo, como la CT-1 (Pennica et al., 1996a; Sheng et al., 1996), el GDNF (Henderson et al., 1994a; Oppenheim et al., 1995) o el FGF-5 (Hughes et al., 1993a, 1993b).

En el caso de las NT's (BDNF, NT-3 y NT-4/5), en nuestro laboratorio hemos obtenido evidencias de que no son responsables de las acciones neurotróficas derivadas del músculo esquelético, al menos en las fases iniciales del proceso de muerte neuronal programada (Soler et al., 1997; véase Apartados 9.3 y 9.4). Asimismo, Prevetie et al. (1994) han demostrado que, a diferencia del MEX, las NT's no son capaces de rescatar MTN's cuando la muerte fisiológica es potenciada mediante la eliminación de sus dianas de inervación. Las MTN's embrionarias expresan moléculas de ARNm para TrkB y TrkC (Ernfors et al., 1993; Henderson et al., 1993a; Koliatsos et al., 1993), aunque no aparecen en las MTN's espinales hasta las fases tardías del proceso de muerte fisiológica (McKay et al., 1993). Por otra parte, en animales que no

expresan moléculas funcionales de BDNF, NT-3 o NT-4/5 no es posible detectar ninguna diferencia en los números de MTN's respecto a los animales normales (Ernfors et al., 1994a, 1994b; Jones et al., 1994; Conover et al., 1995; Liu et al., 1995).

La presencia del receptor TrkB en las dendritas sugiere que las MTN's también podrían recibir un aporte de BDNF desde sus aferencias en el tronco encefálico y la médula espinal (Yan et al., 1994). En concreto, durante el desarrollo embrionario de los roedores es posible detectar la expresión de esta NT en el subgrupo de neuronas de los ganglios espinales con un diámetro mediano a grande (Ernfors y Persson, 1991; Schecterson y Bothwell, 1992). Estas neuronas, de tipo propioceptivo, inervan los husos neuromusculares en la periferia y forman monosinapsis con las MTN's del asta anterior de la médula espinal, constituyendo su principal fuente de BDNF en el SNC. A su vez, las neuronas propioceptivas de los ganglios espinales embrionarios dependen de la NT-3 (Ernfors et al., 1994b; Fariñas et al., 1994; Klein et al., 1994), que probablemente obtienen a partir de los husos neuromusculares (Coprav y Brouwer, 1994; Oakley et al., 1995) y las MTN's espinales (Maisonpierre et al., 1990b; Ernfors y Persson, 1991; Ernfors et al., 1991; Schecterson y Bothwell, 1992; Henderson et al., 1993a; Mudge, 1993). Por otro lado, no se puede excluir la posibilidad de que la NT-3 derivada de las propias MTN's espinales actúe de una forma autocrina o paracrina estimulando la supervivencia neuronal entre ellas mismas (Mudge, 1993).

En la edad adulta, las MTN's siguen expresando TrkB y TrkC (Henderson et al., 1993a; Yan et al., 1994), mientras que el tejido muscular maduro también expresa ARNm's para el BDNF, la NT-3 y la NT-4/5 (Maisonpierre et al., 1990; Berkemeier et al., 1991; Koliatsos et al., 1993). En concreto, en el período postnatal es posible observar un progresivo incremento de la síntesis del BDNF en el músculo esquelético,

en íntimo paralelismo con la maduración de las uniones neuromusculares (Koliatsos et al., 1993; Lohof et al., 1993). Asimismo, las NT's parecen tener una importante función en los fenómenos de regeneración axonal de las MTN's. En las ratas neonatales, el BDNF, la NT-3 y la NT-4/5 liberados por las células de Schwann son capaces de rescatar las MTN's de la muerte inducida por lesiones de los nervios facial y ciático (Acheson et al., 1991; Meyer et al., 1992; Sendtner et al., 1992a; Yan et al., 1992, 1993; Hughes et al., 1993b; Koliatsos et al., 1993, 1994; Novikov et al., 1995; Schmalbruch y Rosenthal, 1995; Vejsada et al., 1995; Giehl y Tetzlaff, 1996). Además, la NT-4/5 puede favorecer el *sprouting* axonal en las MTN's espinales (Funakoshi et al., 1995).

El CNTF es otra molécula que ha recibido gran atención por su capacidad para estimular la supervivencia de las MTN's embrionarias (Arakawa et al., 1990; Sendtner et al., 1990; Martinou et al., 1992; Vejsada et al., 1995) así como de bloquear la muerte fisiológica de las MTN's durante el desarrollo embrionario (Wewetzer et al., 1990; Oppenheim et al., 1991). No obstante, el CNTF endógeno no parece estar implicado en la regulación de la supervivencia de las MTN's durante el desarrollo embrionario, dado que es una proteína citosólica (Lin et al., 1989; Stöckli et al., 1989) y no se expresa en el tejido muscular embrionario (Stöckli et al., 1989, 1991). El análisis de ratones (Masu et al., 1993) y humanos (Takahashi et al., 1994) homocigotos para mutaciones nulas del gen *CNTF* demuestra como las MTN's completan su desarrollo embrionario con una aparente normalidad en ausencia del CNTF. Paradójicamente, los animales carentes del CNTFR α presentan déficits profundos en todas las poblaciones de MTN's examinadas, incluyendo las espinales y las de los núcleos del tronco encefálico (DeChiara et al., 1995).

Estas observaciones, sorprendentes al compararlas con los efectos de la delección del gen *CNTF* sobre las MTN's, sugiere la existencia de un factor neurotrófico CNTF-oide esencial para el desarrollo embrionario normal de la población neuronal motora (DeChiara et al., 1995). De hecho, las MTN's del SN embrionario expresan niveles elevados de CNTFR α (MacLennan et al., 1996). Las acciones del CNTF administrado exógenamente sobre las MTN's embrionarias simplemente podrían reflejar las acciones fisiológicas de este factor CNTF-oide aún por identificar. Parece improbable que alguno de los miembros conocidos de la familia de citocinas del CNTF sea el ligando alternativo que utiliza el CNTFR α , especialmente si se considera que la neutralización de los genes de algunos de dichos factores no origina fenotipos similares al de los ratones deficientes de CNTFR α (Stewart et al., 1992; Escary et al., 1993; Kopf et al., 1994; Stahl y Yancopoulos, 1994; Pennica et al., 1995a). El CDF/LIF, emparentado con el CNTF, también parece ser necesario para el desarrollo embrionario normal de las MTN's espinales y de los núcleos craneales, puesto que la inactivación del gen que codifica este factor conlleva la pérdida de mayor del 35% de las MTN's faciales, el 40% de las MTN's espinales y el 50% de las neuronas motoras del núcleo ambiguo (Li et al., 1995c).

En la edad adulta, el CNTF está claramente involucrado en los mecanismos de regeneración nerviosa (revisado en Apartado 4.2). Este factor es capaz de rescatar MTN's faciales y espinales de la muerte inducida por axotomía (Sendtner et al., 1990; Li et al., 1994; Vejsada et al., 1995) y su administración sistémica mejora los déficits funcionales y los cambios citopatológicos en modelos animales de disfunción neuromuscular (Helgren et al., 1992; Sendtner et al., 1992b; Mitsumoto et al., 1994a, 1994b; Sagot et al., 1995). Asimismo, el análisis morfométrico de las MTN's espinales de ratones portadores de una delección del gen *CNTF* demuestra una progresiva atrofia y degeneración a partir de la 8ª

semana postnatal (Masu et al., 1993), quizás en relación con la participación del CNTF en la regulación de los fenómenos de *sprouting* y estabilización de los contactos sinápticos de las MTN's con el músculo diana (Gurney et al., 1992; Helgren et al., 1992; Kwon y Gurney, 1994). Además, el CNTF tiene un efecto miotrófico directo, logrando una reducción de la atrofia muscular en relación con la denervación al actuar sobre los receptores para el CNTF presentes en la superficie de los miotubos (Helgren et al., 1994).

Un hecho común a todos los agentes neurotróficos conocidos con actividad sobre las MTN's es que sólo mantienen la supervivencia de una proporción de las MTN's. Asimismo, se han descrito múltiples ejemplos de aditividad o incluso sinergismo entre los factores neurotróficos (Arakawa et al., 1990; Hughes et al., 1993a, 1993b; Wong et al., 1993; Kato y Lindsay, 1994; Vejsada et al., 1995). Una posible explicación *in vivo* para la heterogeneidad de respuestas de las MTN's a los diferentes factores neurotróficos observada *in vitro* sería la existencia de varias subpoblaciones de MTN's con requerimientos neurotróficos distintos o parcialmente solapados, de forma similar a lo que ocurre con las neuronas sensoriales de los ganglios espinales (Snider, 1994) o nodosos (Conover et al., 1995). Aunque *in vitro* las MTN's puedan responder a múltiples agentes neurotróficos, parece lógico que *in vivo* los diferentes factores tróficos sólo estén disponibles para determinadas subpoblaciones de MTN's en base a su distribución en los diferentes compartimentos tisulares alrededor de las MTN's. Por último, la diversidad de factores neurotróficos con efectos sobre las MTN's también podría reflejar la participación de las aferencias en la regulación de la supervivencia y/o la diferenciación de las MTN's durante el desarrollo embrionario (Okado y Oppenheim, 1984), tradicionalmente infravaluada.

Las MTN's también experimentan una transición en sus requerimientos neurotróficos durante el desarrollo embrionario, de forma que parecen depender de diferentes agentes tróficos antes, durante y después del período de muerte fisiológica. En los estadios iniciales de la embriogénesis del pollo, las MTN's presentan un período de independencia neurotrófica (Méttlng et al., 1995). Tras una etapa en la que responden a la NT-3 con una diferenciación acelerada (Averbuch-Heller et al., 1994), las MTN's cultivadas adquieren su capacidad para responder a los factores neurotróficos del tejido muscular, probablemente durante el período de invasión de los tejido diana (Méttlng et al., 1995). Inmediatamente antes de iniciarse el período de muerte fisiológica, las MTN's parecen depender para su supervivencia más de los astrocitos inmaduros que de los factores liberados por el tejido muscular (Eagleson et al., 1985; Eagleson y Bennett, 1986). Posteriormente, a lo largo del desarrollo embrionario restante e incluso en la etapa postnatal, las MTN's probablemente desarrollan requerimientos tróficos adicionales para su supervivencia.

En conjunto, todas estas observaciones sugieren que los requerimientos tróficos de las MTN's pueden llegar a ser muy complejos. Durante el período de muerte neuronal fisiológica la supervivencia de las MTN's aparentemente depende de factores derivados del músculo (como el GDNF, el FGF-5, la CT-1, el CDF/LIF o un factor CNTF-oide desconocido) y en parte de factores sintetizados por las neuronas aferentes del SNC (como el BDNF). Las NT's BDNF, NT-3 y NT-4/5 parecen intervenir en las fases tardías del proceso de muerte fisiológica (McKay et al., 1993). A medida que progresa el desarrollo embrionario del SN, primero, y en la edad postnatal y adulta, después, intervienen ya otros factores neurotróficos adicionales con capacidad para influir sobre la supervivencia y la función de las MTN's (como el TGF β , los IGF's y la insulina, el CDF/LIF, el FGFa y el FGFb, los PDGF- α y - β o la IL-6) que

podrían ser responsables de una diversidad de funciones, como la regulación del *sprouting* de los axones motores en la periferia o la eliminación de la inervación polineuronal generada en etapas más precoces. En la edad postnatal, en respuesta a la lesión de un tronco nervioso las células de Schwann inician la síntesis de otros factores adicionales (como el CNTF o el BDNF) que podrían ser importantes en la regeneración de los axones motores.

11.9 Los factores neurotróficos y las enfermedades neurodegenerativas

Existen grandes expectativas sobre el futuro impacto de los conocimientos actuales sobre el neurotrofismo en la Neurología clínica. Hay una amplia variedad de patologías neurológicas caracterizadas por una pérdida gradual de subpoblaciones o grupos específicos de neuronas. Entre ellas, se incluyen la enfermedad de Alzheimer (en la que se degeneran las neuronas colinérgicas de los núcleos basales y septales del cerebro), la enfermedad de Parkinson (con afectación de las neuronas dopaminérgicas del sistema nigroestriado), la esclerosis lateral amiotrófica (ELA) (caracterizada por la degeneración de las MTN's espinales y de los tractos córtico-espinales), la atrofia muscular espinal de Werdnig-Hoffman (que cursa con una deplección progresiva de las MTN's espinales), y diversas formas de degeneraciones cerebelosas y neuropatías sensitivas y motoras adquiridas y hereditarias (como, por ejemplo, la neuropatía sensorial hereditaria tipo III o distonía familiar, caracterizada por una degeneración de las neuronas de los ganglios sensoriales y autonómicos).

En general, la pérdida de células neuronales que se produce en estas patologías es de tipo apoptótico, no causando una respuesta inflamatoria. Diversos neurobiólogos han sugerido la posibilidad de que la etiopatogenia de estas enfermedades implique una deficiencia de un

determinado factor neurotrófico y/o alteraciones a nivel de receptor o de la señalización intracelular, que producirían un compromiso de la función neuronal, atrofia o, incluso, la muerte neuronal. Sin embargo, hasta la fecha no se ha conseguido establecer con claridad la relevancia de deficiencias de factores neurotróficos concretos en patologías neurológicas específicas. Por contra, se han identificado algunos mecanismos fisiopatogénicos alternativos. Por ejemplo, existe una forma de ELA hereditaria secundaria a una mutación del gen que codifica la SOD (Deng et al., 1993; Rosen et al., 1993), con la consiguiente capacidad de las células para eliminar los ROR's.

En la enfermedad de Alzheimer, el péptido β -amiloide parece tener un gran protagonismo, siendo capaz de inducir la apoptosis de células neuronales (Loo et al., 1993; Takashima et al., 1993). Por otra parte, recientemente se ha caracterizado un gen denominado *NAIP* (Roy et al., 1995), cuya mutación podría ser responsable de la muerte de MTN's en individuos afectados de atrofia muscular espinal de Werdnig-Hoffman. Asimismo, se ha relacionado esta enfermedad de la infancia con una deficiencia en la producción de la actividad trófica para las MTN's presente en el músculo esquelético (Henderson et al., 1981), habiéndose llegado a sugerir que es el resultado de una potenciación del fenómeno de muerte neuronal fisiológica durante el desarrollo embrionario (Gamstrop y Sarnat, 1984).

De forma global, se ha postulado que diversos mecanismos, como el *stress* oxidativo, la toxicidad del Ca^{2+} , alteraciones de la función mitocondrial, la excitotoxicidad o la privación de factores de supervivencia, contribuyen a la patogénesis de todas estas patologías neurodegenerativas (Ziv et al., 1994). Por tanto, parece lógico suponer que los mecanismos básicos responsables de la degeneración apoptótica

sean similares o incluso idénticos a los que operan durante el desarrollo embrionario.

En los últimos 15 años, se ha publicado una larga serie de experimentos *in vitro* e *in vivo* que demuestran la capacidad de los factores neurotróficos para neutralizar la acción letal de diferentes noxas. Estos resultados han constituido la base para el empleo de factores neurotróficos en el tratamiento de enfermedades neurodegenerativas (Hefti, 1994; Lindsay et al., 1994). Se han iniciado ensayos clínicos utilizando la administración sistémica o intratecal de factores neurotróficos en pacientes con ELA, enfermedad de Alzheimer, neuropatía diabética y otras neuropatías periféricas (Barinaga, 1994; Brewster et al., 1994). Por otra parte, los efectos de los factores neurotróficos sobre el crecimiento neurítico y su habilidad para prevenir la muerte neuronal tras lesiones mecánicas de los troncos nerviosos sugieren que estas moléculas podrían ser útiles para estimular la regeneración nerviosa tras las lesiones traumáticas.

Se han diseñado tres estrategias para aumentar las concentraciones de factor neurotrófico a nivel tisular: el aporte exógeno (vía intratecal o mediante implantes de una matriz polímera impregnada del factor), el trasplante de líneas celulares diseñadas para secretar NT's, y el aumento de la producción endógena de un determinado factor neurotrófico. También se podría administrar moléculas modificadas, fragmentos activos o, incluso, moléculas agonistas no peptídicas con capacidad para atravesar la barrera hematoencefálica y de ser administrados de formas más convencionales, aunque esto aún parece lejano en el tiempo.

CONCLUSIONES

Primera: La técnica de purificación celular mediante sedimentación sobre un gradiente de metrizamida permite obtener de forma reproducible y eficiente una población pura (>95%) de motoneuronas embrionarias de 6 días de edad, según criterios morfológicos, bioquímicos e inmunocitoquímicos.

Segunda: *In vitro*, las motoneuronas espinales embrionarias son estrictamente dependientes de la(s) actividad(es) trófica(s) contenida(s) en el tejido muscular para su supervivencia.

Tercera: *In vitro*, la muerte de las motoneuronas espinales embrionarias inducida por privación de extracto muscular es apoptótica, según sugiere el estudio morfológico a nivel nuclear y citoplasmático de este fenómeno, así como la detección de un patrón de fragmentación oligonucleosomal del ADN en las motoneuronas “comprometidas” a la muerte celular.

Cuarta: *In vitro*, en las motoneuronas espinales embrionarias privadas de extracto muscular se observa una activación transitoria del programa de muerte celular.

Quinta: El arabinósido de citosina induce la muerte apoptótica de las motoneuronas espinales embrionarias mediante su interferencia con un proceso específico dependiente de 2'-deoxicitidina. Este hecho constituye una evidencia de la implicación del metabolismo de las purinas y pirimidinas en la supervivencia de las células neuronales.

Sexta: Durante el desarrollo embrionario del embrión de pollo, las motoneuronas espinales presentan en su superficie receptores TrkB y TrkC. Su activación por los correspondientes ligandos, BDNF y NT-3,

comporta la fosforilación y, presumiblemente, activación de las kinasas citosólicas MAPK's.

Séptima: Las motoneuronas espinales modifican sus requerimientos tróficos durante el desarrollo embrionario; mientras que en las etapas iniciales del período de muerte fisiológica no presentan receptores Trk en su membrana plasmática, posteriormente adquieren la capacidad de responder al BDNF, a la NT-3 y a la NT-4/5 al iniciar la síntesis de los receptores TrkB y TrkC, respectivamente.

Octava: La autofosforilación de los receptores Trk es necesaria para las respuestas de supervivencia y diferenciación neuronal, aunque de forma diferente; Mientras que el grado de autofosforilación del receptor Trk se correlaciona con la respuesta de diferenciación, la señalización de la supervivencia sólo precisa niveles muy reducidos de fosforilación de dicho receptor. Este hecho probablemente refleja que las vías de transducción implicadas en la mediación de la supervivencia y la diferenciación neuronal divergen muy pronto tras la activación de los receptores Trk.

Novena: *In vitro*, la despolarización crónica estimula la supervivencia de las motoneuronas espinales embrionarias, aparentemente a través del incremento de la $[Ca^{2+}]_i$ en relación con la activación de canales de Ca^{2+} voltaje-dependientes tipo L.

Décima: La despolarización crónica de las motoneuronas espinales comporta la fosforilación a nivel de residuos de tirosina de las MAPK's, reflejando la activación de la vía de transducción p21ras-MAPK. Este mecanismo es independiente de la estimulación de los receptores Trk presentes en la superficie de las motoneuronas.

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